Amendments to the Specification

Additions are indicated by underlining (underlining), and deletions are indicated by strikethrough (–).

Please replace paragraph 0019 spanning pages 6-9 with the following amended paragraph:

[0019] In the drawings the figures show as

(figure 1) (A) anti-*Xenopus* TPX2 Western blot (upper panel) and anti-*Xenopus* Aurora-A Western blot (lower panel) of GST (glutathione S transferase) (lanes 1 and 2), GST *Xenopus* TPX2 (lanes 3 and 4) or GST *Xenopus* TPX2(1-39) (lanes 5 and 6) which proteins were incubated in *Xenopus* cytostatic factor (CSF) arrested extracts in the presence or absence of RanQ69L-GTP and immunoprecipitated with GST antibody-coated beads;

(B) anti-GST Western blot (upper panel) and anti-human Aurora-A Western blot (lower panel) of GST (lane 1), GST TPX2(1-43) (lane 2) or GST TPX2(15-43) (lane 3) proteins that were incubated in mitotic HeLa cell extract and immunoprecipitated with GST antibody-coated beads;

(C) autoradiography of the SDS-PAGE gel (left panel) and the corresponding Coomassie-stained gel (right panel) after *in vitro* phosphorylation (γ^{32}P-ATP) of histone H3 by human Aurora-A in the presence of full-length TPX2, GST TPX2(1-43) or GST TPX2(15-43) (lanes 2, 3 and 4 respectively);

(D) much of the phosphorylation signal in GST after *in vitro* phosphorylation (γ^{32}P-ATP) of TPX2(1-43) by Aurora-A (lane 1) followed

by TEV cleavage (lane 2);

(E) an anti-human Aurora-A Western blot (upper panel) and an anti-phosphoAurora-A Western blot (lower panel) after phosphatase PP1 treatment of human Aurora-A in the absence or presence of full-length TPX2, GST TPX2(1-43) or GST TPX2(15-43) followed by detection of Aurora-A by a polyclonal antibody (upper panel) and an antibody specific for Aurora-A phosphorylated at $Thr288^{AUR}$ (lower panel);

(figure 2) (A) an *in vitro* pull-down assay with respect to the binding of full-length Aurora-A, AuroraΔN or AuroraΔN(D274N) to GST TPX2(1-43) (lanes 4, 5 and 6), and to GST (lanes 1, 2 and 3);

(B) an anti-phospho Aurora-A Western blot of wild-type Aurora(ΔN) and the D274N mutant when expressed in *E. coli*.

(C) autoradiograph for detecting *in vitro* phosphorylation of histone H3 by Aurora(ΔN) in the presence or absense of TPX2(1-43) (lane 2 compared to lane 1), the cleaved (lane 2) or uncleaved (lane 3) GST TPX2(1-43) fusion protein;

(D) Sequence alignment of TPX2 N-terminal domain from human (*H*) [SEQ ID NO: 1], *Xenopus* (*X*) [SEQ ID NO: 2] and puffer fish (*F*) [SEQ ID NO: 3], secondary structure elements being shown above the sequences *in red* (upstream extended stretch) and *pink* (downstream helical stretch), and intervening residues not modelled being marked with a dotted line;

(E) Sequence alignment of Aurora-A kinase catalytic domain from three vertebrate species that contain TPX2 (human, *H.AUR-A* [SEQ ID NO: 4] ; *Xenopus*, *X.AUR-A* [SEQ ID NO: 5] ; puffer fish, *F.AUR-A* [SEQ ID NO: 6]), two invertebrates that do not contain TPX2 (*Drosophila, D.AUR-A* [SEQ ID NO: 7]*; C.elegans*, *C.AUR-A* [SEQ ID NO: 8]) together with human and *Xenopus* Aurora-B (*H.AUR-B* [SEQ ID NO: 9] , *X.AUR-B* [SEQ ID NO: 10]) and vertebrate cAPK [SEQ ID NO: 11], wherein Aurora-A

secondary structural elements are labelled above the alignment, the phosphorylated Thr288 (human numbering) is shown, and residues that interact with 7-21^{TPX} or 30-43^{TPX} being indicated by filled or open circles respectively;

(figure 3) ribbon style drawings of the structure of Aurora-A bound to TPX2 as

(A) a view of the complex between the catalytic domain of human Aurora (AuroraΔN) and the N-terminal domain of TPX2 shown in typical kinase orientation, an upstream stretch of TPX2 binding at the N-terminal lobe of Aurora-A, and a downstream stretch binding between the two lobes, and a dotted line marking the approximate path of the linker connecting the two TPX2 stretches (disordered and not modeled);

(B) a view of the complex after a 180° rotation about the vertical axis in respect to view in panel A showing more clearly the two stretches of TPX2 that bind to Aurora-A;

(C) the upstream stretch of TPX2 (residues 7-21^{TPX}) that binds at a hydrophobic surface groove present in the N-terminal lobe of the kinase, wherein details of the extensive interactions are shown in the same orientation as in panel B;

(D) the downstream helical stretch of TPX2 (residues 30-43^{TPX}) that binds Aurora-A near helix αC and the activation segment, close to but not directly in contact with phospho-Thr288^{AUR}, wherein details of interactions being shown in the same orientation as in panel B and C.

(figure 4) ribbon style drawings of conformational states of phosphorylated Aurora-A in the presence and absence of TPX2 as

(A) an overlay showing that the structures of Aurora-A when bound to TPX2 and when unbound are closely superposable at the position of active site residues and of helix αC, but diverge at the activation segment between residues His280^{AUR} and Leu293^{AUR}, wherein Phospho-Thr288^{AUR}

points inwards in the TPX2-bound structure and outwards in the kinase alone structure;

(B) an illustration of conformational changes upon TPX2 binding, according to which the activation segments of the kinase alone structure (left panel) and of the TPX2-bound structure (right panel) are shown in a view rotated by approximately 90° with respect to panel A, and TPX2 binding results in the reorganization of the activation segment, with a 10 Å movement of $Thr288^{AUR}$;

(C) a schematic representation of the molecular mechanism of TPX2-mediated activation of Aurora-A, according to which the upstream stretch of TPX2 anchors the regulator to the N-terminal lobe of the kinase and the downstream stretch (helix) hooks the activation segment triggering a lever-arm like movement, where rotations at $His280^{AUR}$ and $Pro282^{AUR}$ pull on $Thr288^{AUR}$;

(figure 5) the structure coordinates of phosphorylated human Aurora-A(ΔN) kinase (table A);

(figure 6) the structure coordinates of phosphorylated human Aurora-A(ΔN)/TPX2(1-43) complex (table B).

Please replace paragraph 00128 on page 29 with the following amended paragraph:

[00128] The amino acid radicals aa may be any amino acid. Preferably said amino acid radicals are selected to mimick – together with the connecting amino acid - a portion of TPX2 that binds to Aurora-A. Said portion of TPX2 is in particular a portion comprising the amino acid sequence from residues 7 to 21, preferably 8 to 19 (compare Fig. 3C) or a fragment thereof. Accordingly, suitable peptides may have the sequence Tyr-Xaa1-Tyr-Xaa2-Ala-Pro-Xaa3-Xaa4-Phe-Xaa5-Xaa6-Phe [SEQ ID NO: 12] or a portion thereof, wherein Xaa1-6 may be any amino acid radical. Xaa1 preferably is a serine radical or a similar amino acid. Xaa2 preferably is an aspartate radical or a

similar amino acid. Xaa3 preferably is a serine radical or a similar amino acid. Xaa4 preferably is an aspartate radical or a similar amino acid. Xaa5 preferably is an isoleucine radical or a similar amino acid. Xaa6 preferably is an asparagine radical or a similar amino acid. A particularly preferred portion is the sequence Tyr-Xaa1-Tyr-Xaa2-Ala-Pro-Xaa3-Xaa4-Phe [SEQ ID NO: 13]. By similar amino acid is meant an amino acid that is considered to result in a conservative change of the peptide's structure when it replaces the amino acid to which it is similar. For instance, aspartate is similar to glutamate. The peptide preferably has a length of 3 to 15, more preferably of 4 to 10 and ~~advantagously~~ advantageously of 5 to 8 amino acid, the sum of n + m thus being 2 to 14, more preferably of 3 to 9 and ~~advantagously~~ advantageously of 4 to 7, respectively.

Please replace paragraph 00172 on page 41 with the following amended paragraph:

[00172] The upstream stretch of TPX2 has a mostly extended conformation, with a kink in the middle induced at a proline residue ($Pro13^{TPX}$) (for details see Figure 3C). The conserved segment $^{8}YSYDAPS^{14}$ [SEQ ID NO: 14] (Figure 2D) is engaged in extensive main-chain and side-chain interactions with Aurora-A. In particular, $Tyr8^{TPX}$, $Tyr10^{TPX}$ and $Ala12^{TPX}$ tightly nestle into a hydrophobic groove between the β-sheet, helix αB and helix αC. An adjacent hydrophobic groove accommodates the side chains of TPX2 residues from $Phe16^{TPX}$ to $Phe19^{TPX}$. The N-terminal residues of the Aurora-A catalytic core make key contributions to this interface, in particular with $Arg126^{AUR}$ forming a cation-π interaction with $Phe16^{TPX}$.